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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,335	01/02/2002	Ronnie C. Hanecak	ISIS-4976	7737

34138 7590 03/25/2004

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,335	HANECAK ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

35 USC 102 Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 are rejected under 35 U.S.C. 102(e) as being anticipated by West et al.

Applicants claim a chemically modified oligonucleotide (i.e. having at least one phosphorothioate linkage) having no more than about 27 nucleic acid base units and having the sequence $(N_xG_{3-4})_QN_x$ wherein X is 1 to 8 and Q is 1 to 6 wherein said oligonucleotide modulates mammalian telomere length.

West et al. (U.S. Patent 5,489,508, issued 2/6/96, effective filing date 5/13/92, see whole document, particularly Examples 1 and 2 on columns 22-24) teach an oligonucleotide (TTAGGGTTAGGG) which modulates telomere length in mammalian cells wherein said oligonucleotide is encompassed within applicants' recited formula. West et al. also recites that the oligonucleotide can be modified (i.e. phosphorothioates) to increase stability. Therefore West et al. teaches the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over West et al. (as applied above) in view of Bischofberger et al.

Applicants claim a chemically modified oligonucleotide which has at least one 2' modification of the sugar and is capable of modulating telomere length.

West et al. teaches the claimed invention with the exception of reciting a oligonucleotide having at least one 2' modification of the sugar. West et al. teaches that modified oligonucleotides can be used to enhance stability and recites several examples of chemically modified oligonucleotides. The question therefore is would the ordinary skilled artisan have been motivated to choose 2' modifications of the sugar as the specific modification.

Bischofberger et al. (U.S. Patent 5,633,360, issued 5/27/97, filed 4/14/92, see whole document, particularly column 5, lines 32-42) recites the generation of oligonucleotides having 2' modifications of the sugar.

The ordinary skilled artisan, seeking to choose a type of modified oligonucleotide for use in the method of West et al. for modulating telomere length, would have been motivated to incorporate a 2' modification of the sugar because Bischofberger et al. teaches that oligonucleotides modified at the 2' position on the sugar moiety are preferred for delivery to cells because of their increased lipophilicity compared to unmodified sugars. It would have been obvious for the ordinary skilled artisan to do this because Bischofberger et al. teaches that oligonucleotides modified at the 2' position on the sugar have increased lipophilicity and hence said oligonucleotides have increased passive cell membrane permeation ability. Since modifications of the 2' position of the sugar were well known in the art, as exemplified by Bischofberger et al., and were known to increase the permeability of oligonucleotides across cell membranes, the skilled artisan would have been motivated to use these modifications in any method for delivering oligonucleotides into cells, such as the method disclosed by West et al. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over West et al. (as applied above) in view of Padmapriya et al.

Applicants claim a modified oligonucleotide which is a chimeric oligonucleotide and is capable of modulating telomere length.

West et al. teaches the claimed invention with the exception of reciting an oligonucleotide which is a chimeric oligonucleotide.

Padmapriya et al. (U.S. Patent 5,929,226, issued 7/27/99, effective filing date 7/27/92, see whole document, particularly column 3, lines 39-57) recites the generation and use of chimeric oligonucleotides.

One of ordinary skill in the art, seeking to choose a type of oligonucleotide modification to use in the disclosure of West et al., would have been motivated to generate chimeric oligonucleotides because the oligonucleotides used by West et al. are to be used in cells *in vitro* and *in vivo* and would therefore need to be resistant to nucleases; Padmapriya et al. teaches that chimeric oligonucleotides are resistant to nucleolytic degradation and that this makes them particularly useful for oligonucleotide based therapies. It would have been obvious for the ordinary skilled artisan to generate chimeric oligonucleotides for use as modulators of telomere length (as recited by West et al.) because Padmapriya et al. teach that chimeric oligonucleotides have desirable characteristics such as increased stability and resistance to nuclease degradation wherein said characteristics make them particularly useful for any oligonucleotide based therapies. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that the ordinary

skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim methods (*in vitro* and *in vivo*) of modulating telomere length of a mammalian chromosome, methods for inhibiting division of a malignant mammalian cell and methods for modulating the effects of aging of a mammalian cell comprising contacting the chromosomes in a target cell (*in vitro* or *in vivo*) with a modified oligonucleotide having no more than about 27 nucleic acid base units and having the sequence $(N_xG_{3-4})_QN_x$. Applicants also claim said chemically modified oligonucleotides. The oligonucleotide claims (claims 1-4) are included in this rejection because the only disclosed uses for oligonucleotides which modulate mammalian cell telomere length involve therapy for treatment of cancer or inhibition of aging. Applicants present no uses for a method of modulating telomere length of cells *in vitro*.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reaches by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art. The art in the area of use of oligonucleotides which can modulate telomere length as therapeutic agents for treatment of cancer and diseases associated with aging must be considered unpredictable. *In vitro*, the ability of oligonucleotides to modulate telomere length is unpredictable and appears to depend on the specific cell line involved and the length of the telomeres in the cells. *In vivo*, the ability of oligonucleotides to modulate telomere length so as to provide an effective therapy for treatment of cancers is untested. Indeed, more than 10 years after the effective filing date of applicants' invention, those of skill in the art are **still contemplating the beginning** of *in vivo* clinical trials to evaluate whether therapies for cancer treatment involving molecules which modulate telomere length have any efficacy in patients (See for example Rezler et al., Annu. Rev. Pharmacol. Toxicol., 2003, Vol. 43, pp. 359-379; Helder et al., Cancer Investigation, 2002, Vol. 20(1), pp. 82-101; Saretzki, Cancer Letters, 2003, Vol. 194, pp. 209-219). Methods of inhibiting the effects of aging of cells *in vivo* using oligonucleotides which can modulate telomere length has,

as far as the examiner has been able to determine, not even been seriously contemplated.

With regard to using oligonucleotides *in vivo*, many generic problems exist with regard to delivery of the oligonucleotides to the appropriate tissues, unpredictability in getting the oligonucleotides into the appropriate cells in sufficient quantities, the lack of reproducibility of data, the lack of correlation between results seen in animal models and human efficacy, etc. The problems associated with use of oligonucleotides *in vivo* is exemplified in the antisense oligonucleotide art (See for example, Nature Biotechnology, 1997, Vol.15, pp. 519-524 and Branch, TIBS, 1998, Vol. 23, pp. 45-50).

State of the art. The state of the art with regard to use of oligonucleotides directed to modulating telomere length for the treatment of cancers or other diseases was at the time of applicants' invention, nil.

Number of working examples. Applicants provide no examples of the claimed invention.

Amount of guidance provided. Applicants provide examples whereby telomere length in immortalized cell lines and human xenografts in nude mice was reduced after administration of the instantly recited oligonucleotides. However, the relevance of this data to treatment of cancer or treatment of aging is unclear. Indeed, more than 10 years after the effective date of applicants' invention, the state of the art with regard to actual *in vivo* testing of oligonucleotides which can modulate telomere length for treatment of cancer has still not progressed beyond the *in vitro* and animal model stage. Clearly, the relevance of the *in vitro* and animal model data presented by applicants to

actual *in vivo* efficacy for treatment of cancer or aging is, many years after the filing date of applicants' invention, still very unclear.

Nature of the invention. The invention involves use of oligonucleotides to modulate telomere length in cells so as to inhibit growth of malignant cells or inhibit aging.

Scope of the invention. The invention reads broadly on use of oligonucleotides to inhibit growth of any malignant cells or to modulate the effects of aging of any mammalian cells *in vitro* or *in vivo*. The claims must therefore be considered broad.

Level of skill in the art. The level of skill in the oligonucleotide and telomere art is high; however, given the broad scope of the claims, the lack of guidance in practicing the claimed invention, the poorly developed state of the art and the high level of unpredictability in the art, it must be considered that the skilled artisan would have needed to have conducted essentially trial and error experimentation in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have needed to have conducted undue and excessive experimentation in order to practice the claimed invention.

It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (enablement) and 35 USC 102(e). While these rejections may seem contradictory, they are not because each is based upon a different legal analysis, i.e. sufficiency of the disclosure of the instant application to support claims under 35 USC

112, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783 (CCPA 1969)). In the instant case, the claimed oligonucleotides are disclosed in the prior art and are hence anticipated. However, since the instant specification does not provide an enabled use for the same oligonucleotides, said oligonucleotides are legitimately rejected under lack of enablement

35 USC 112, 2nd Paragraph Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is vague in the recitation of the phrase "...2' modification of the sugar." Because it is unclear what "the sugar" refers to, there is no antecedent basis for this term.

Double Patenting Rejections

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-21 and 23-27 of U.S. Patent No. 5,952,490 (hereafter the '490 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because the oligonucleotides claimed in the '490 patent are encompassed within the instantly claimed subject matter. The modified oligonucleotides claimed in the '490 patent are species encompassed within the broad formula recited in claim 1. For example, the phosophorothioate oligonucleotide TTGGGGTT claimed in the '490 patent is encompassed within the instant formula and is specifically contemplated by applicants as a oligonucleotide expected to result in modulation of telomere length (see specification, p. 14, Table 1). Likewise, the modified oligonucleotides recited in the '490 claims as having the formula TxG4Ty wherein x and y can be 2 or 3 or claims reading on oligonucleotides of no more than about 27 nucleotides and comprising at least two GGG sequences and a sufficient number of flanking sequences to modulate telomere length are encompassed within the instant formula. The claims of the '490 patent would anticipate the claimed invention.

Miscellaneous

Applicants submitted on 8/16/02, in response to a Notice to File Missing Parts of Application mailed 2/12/02, a Declaration signed by the inventors; however, the Declaration was not scanned into the electronic file wrapper. Applicants are requested to resubmit a copy of the Declaration with their response to this Office Action.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
March 21, 2004

DAVID GUZO
PRIMARY EXAMINER